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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 14

Application Number: 09/912,717
Filing Date: July 24, 2001
Appellant(s): HILLMAN ET AL.

Richard C. Ekstrom and Joel Harris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/27/03

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: The enablement and written description rejections of claims 46 and 54-59 under 35 U.S.C. 112 first paragraph, are hereby withdrawn in view of Appellants' argument that the specification teaches how to make and use antibodies which binds specifically to SEQ ID NO: 1.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 45, 47, 49, 50, 52, 60 and 61 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is partially correct.

Claims 45-63 are pending.

Claims 45, 47, 49-50, 52, 60 and 61 are on appeal.

Claims 46 and 54-59 are allowed.

Claims 48, 51, 53 and 62-63 are withdrawn.

(9) Prior Art of Record

6,180,370 B1 Queen 1-2001

Kuby, J. "Antigen" in Immunology, Second Edition, W.H. Freeman and Company, New York, 1994

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45, 47, 49-50, 52, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 as set forth in claim 46 and 54-59 for diagnostic assays, **does not** reasonably provide enablement for (1) *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino

acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity, (2) the antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5- carboxylate reductase activity wherein the antibody is any chimeric antibody, any single chain antibody, any Fab fragment, any F(ab')2 fragment or any humanized antibody, (3) *any* composition comprising *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity and an acceptable excipient, (4) *any* composition comprising *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity and an acceptable excipient wherein the antibody is labeled, (5) *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 wherein the antibody is a

chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody and a method of producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44).

The specification does not teach how to make and use *any* antibody that binds to *any* polypeptide comprising any "naturally occurring amino acid sequence at least 90% identical" to the amino acid sequence of SEQ ID NO: 1, much less said naturally occurring amino acid sequence having any 1-pyrroline-5-carboxylate reductase activity. There is insufficient guidance as to the binding specificity of the claimed antibody and the immunogen such as the specific amino acid sequence used by appellants to generate antibody that would bind to any naturally occurring amino sequence at least 90% identical to SEQ ID NO: 1 having delta 1-pyrroline-5-carboxylate reductase activity. Further, the term "comprising" is open-ended. It expands the "naturally occurring" amino acid sequence to include additional amino acids at either or both ends. There is no working example in the specification that the claimed antibody binds to any "naturally occurring amino acid sequence at least 90% identical" to the amino acid sequence of SEQ ID NO: 1. Even if the "naturally occurring" amino acid sequence has the same number of amino acids as the claimed sequence of SEQ ID NO: 1 which is 314 amino acids in length, a 90% identity means 10% difference, and that translates to 31 amino acids difference. There is no guidance in the specification as filed with respect which domain (fragment) of the SEQ ID NO: 1 is conserved for enzymatic activity and useful for generating antibody that binds to any natural occurring amino sequence at least 90% identical to SEQ ID NO: 1.

Even if the enzymatic domain is conserved and useful for generating antibody, Kuby *et al,* of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the full-length polypeptide, let alone an antibody that would bind to any natural occurring full-length polypeptide that has at least 31 amino acids difference. Without the specific amino acid residues in the immunogen used by Appellant to make the antibody and the epitope to which the claimed antibody binds, it is unpredictable which undisclosed antigenic determinant will produce antibody such as polyclonal or monoclonal, chimeric, single chain, Fab fragment F(ab')2 fragment or humanized antibody would bind specifically to a polypeptide comprising any naturally occurring amino acid sequence at least

90% identical to the amino acid sequence of SEQ ID NO: 1 and has 1-pyrroline-5-carboxylate reductase activity. Other than the specific antibody that binds to the polypeptide comprising SEQ ID NO: 1, there is insufficient biochemical or structural information about the immunogen used by Appellant that enables the skilled artisan to make the antibody that binds specifically to *any* undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1. Further, the specification discloses only one polypeptide comprising SEQ ID NO: 1, there are no other natural occurring polypeptide at least 90% identical to SEQ ID NO: 1 that has 1-pyrroline-5-carboxylate reductase activity. Without the specific amino acid residues of the undisclosed natural occurring polypeptide at least 90% identical to SEQ ID NO: 1 that has 1-pyrroline-5-carboxylate reductase activity, one skill in the art cannot make the antibody that would binds specifically to said natural occurring polypeptide at least 90% identical to SEQ ID NO: 1, much less for using the antibody for any purpose.

With regard to composition comprising the antibody that binds specifically to any undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxyate reductase activity, since the binding specificity of the antibody and the amino acid sequence of any natural occurring polypeptide at least 90% identical to SEQ ID NO: 1 are not enabled, it follows that any composition any antibody that binds to any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxyate reductase activity for diagnostic use is not enabled. Further, there is no working examples demonstrating that any antibody that binds specifically to SEQ ID NO: 1 would also bind to *any* naturally occurring polypeptide at least 90% identical to SEQ ID NO: 1. Even with chimeric antibody, the '370 patent, of record, teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular).

Given the lack of guidance as to the binding specificity, the antigenic determinant to which the antibody binds and the biochemical structure such as the amino acid sequence of any natural occurring polypeptide at least 90% identical to SEQ ID NO: 1, it would require undue experimentation of one skilled in the art to practice the claimed invention.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Claims 45, 47, 49-50, 52, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity, (2) the antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5- carboxylate reductase activity wherein the antibody is any chimeric antibody, any single chain antibody, any Fab fragment, any F(ab')2 fragment or any humanized antibody, (3) *any* composition comprising *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity and an acceptable excipient, (4) *any* composition comprising *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity and an acceptable excipient wherein the antibody is labeled, (5) *any* isolated antibody which specifically binds to *any* polypeptide comprising *any* "naturally-occurring amino acid sequence at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for treating *any* disease. The specification discloses only an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a

humanized antibody and a method of producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44).

With the exception of the specific antibody that binds specific to the polypeptide comprising SEQ ID NO: 1, there is inadequate written description about the binding specificity, the antigenic determinant of the claimed antibody, and the biochemical structure such as the amino acid sequence of *any* "naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1" to which the claimed antibody binds. Given the lack of a written description of *any* additional representative species of polypeptide such as any "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", any additional representative species of antibody such as polyclonal, monoclonal, chimeric, single chain, humanized, Fab fragment or $F(ab')_2$ fragment thereof that binds to "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Appellants was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Since the structure of the *any* "naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1" to which the antibody binds and the binding specificity of the claimed antibody are not adequately described, it follows that any composition comprising said antibody is not adequately described. It also follows that the antibody wherein said antibody is labeled is not adequately described.

Appellants is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

(11) Response to Argument

Enablement rejection

In the paragraph bridging page 4 and 5 of the Brief, Appellants argue that the specification describes variants to the amino acid sequence of SEQ ID NO: 1 having 1-pyrroline-5-carboxyate reductase activity and antibody which specifically binds to a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity. Through the process of natural selection, nature will have

determined the appropriate amino acid sequence. Given the information provided by SEQ ID NO: 1 (the amino acid sequence of P5CRH) and SEQ ID NO: 2 (the polynucleotide sequence encoding P5CRH), one of skill in the art would be able to routinely obtain "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 using appropriate PCR conditions to identify polynucleotides/polypeptides that already exist in nature.

In response to Appellants' arguments, the claims are drawn to antibody. The specification discloses only one polypeptide comprising SEQ ID NO: 1 having 1-pyrroline-5-carboxyate reductase activity and an antibody that binds specifically to SEQ ID NO: 1 for screening assays. The specification does not teach any other polypeptide such as variants to the amino acid sequence of SEQ ID NO: 1 that has 90% identity to SEQ ID NO: 1 having 1-pyrroline-5-carboxyate reductase activity, much less antibody that binds specifically to said variants of SEQ ID NO: 1. The specification on page 11 defines a "variant" of P5CRH polypeptide (SEQ ID NO: 1) as any amino acid sequence that is altered by one or more amino acid residues such that the variant may have "conservative" or "nonconservative" amino acid changes. However, there is no guidance as to which amino acid within the full-length polypeptide of SEQ ID NO: 1 can be change such as substitution, deletion, insertion or both and whether the antibody made from the polypeptide of SEQ ID NO: 1 would bind to the variant of SEQ ID NO: 1 that is altered by one or more amino acid residues such that the variant may have "conservative" or "nonconservative" amino acid changes. There is no guidance as to the amino acid sequence used by Appellants to generate antibody that would binds not only to SEQ ID NO: 1 but also binds specifically to any undisclosed variant of P5CRH polypeptide (SEQ ID NO: 1). There is no guidance in the specification as filed with respect which domain (fragment) of the SEQ ID NO: 1 is conserved for enzymatic activity and useful for generating antibody that binds to any natural occurring amino sequence at least 90% identical to SEQ ID NO: 1. Even if the enzymatic domain is conserved and useful for generating antibody, Kuby *et al,* of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the full-length polypeptide, let alone an antibody that would bind to any natural occurring polypeptide that has at least 31 amino acids difference (10% of 314).

With regard to one skill in the art would be able to routinely obtain "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1" using appropriate PCR conditions to identify polynucleotides/polypeptides that already exist in nature, there is no guidance as to which primers and PCR condition to obtain "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Further, the use of "percent" in conjunction with any of the various terms that refer to sequence similarity is a problem since sequence identity between two sequences has no common meaning within the art. The term "percent" can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Since the nucleic acid sequence of a polynucleotide determines its protein coding properties, predictability of which changes can be tolerated in a polynucleotide's nucleic acid sequence, the corresponding amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which nucleic acids in the nucleotide sequence, if any are tolerant of modification and which are conserved (ie., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness. However, the problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. Even if the variant of SEQ ID NO: 1 is disclosed, without guidance as to the specific amino acid residues in the immunogen used by Appellant to make the antibody and the epitope to which the claimed antibody binds, it is unpredictable which undisclosed antigenic determinant will produce antibody such as polyclonal or monoclonal, chimeric, single chain, Fab fragment F(ab')2 fragment or humanized antibody would bind specifically to a polypeptide comprising any naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has 1-pyrroline-5-carboxylate reductase activity. Clearly, further research is required to practice the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

At page 6 of the Brief, Appellants argue that conventional methods for making antibodies, such as those described at pages 24-25 of the specification that could be used to make antibodies that specifically bind to the recited polypeptide variants. The skilled artisan would readily know how to use antibodies to a variant of the sequence of SEQ ID NO: 1.

In response to Appellants' arguments, the issue here is not whether one skill in the art could make antibody. The issue here is the binding specificity of the claimed antibody. In the absence of guidance as to the specific amino acid residues in the immunogen used by Appellant to make the antibody and the epitope to which the claimed antibody binds, there is no guarantee of success that the claimed antibody would bind specifically to any variant of SEQ ID NO: 1 such as "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1". Further, there is no guidance as to the structure such as the amino acid sequence of any "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1" in the specification as filed. There is no guidance in the specification as filed with respect which domain (fragment) of the SEQ ID NO: 1 is conserved for enzymatic activity and useful for generating antibody that binds to any natural occurring amino sequence at least 90% identical to SEQ ID NO: 1. Even if the enzymatic domain is conserved and useful for generating antibody, Kuby *et al,* of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the full-length polypeptide, let alone an antibody that would bind to any natural occurring polypeptide that has at least 31 amino acids difference (10% of 314). Since it is unpredictable as to which immunogen would generate antibody that bind specifically to any naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

At page 7 of the Brief, Appellants argue that there is no requirement that the claimed antibodies have the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO: 1. Even if there were such as requirement, the examiner provides no

evidence for differing antibody specificity resulting from a single amino acid substitution of the claimed antibodies.

In response to Appellants' arguments, the specification does not teach how to make much less how to use any antibody that binds to any undisclosed "naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1" having 1-pyrroline-5-carboxylate reductase activity because there is no guidance as to the binding specificity, the epitope to which the antibody binds, and the immunogen such as the specific amino acid sequence used by Appellant to make such antibody that not only binds to SEQ ID NO: 1 but also binds to any undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxylate reductase activity. Further, there is no guidance as to which part of SEQ ID NO: 1 is conserved and useful for generate antibody that binds to other naturally occurring amino acid sequence 90% identical to SEQ ID NO: 1. Even if the enzymatic domain is conserved and useful for generating antibody, Kuby *et al,* of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the full-length polypeptide, let alone an antibody that would bind to any natural occurring full-length polypeptide that has at least 31 amino acids difference. Kuby *et al* further teach that some antibody epitope is composed of nonsequential amino acids, far apart in the primary amino acid sequence that have been brought together by the tertiary folding of the protein while other antibody epitope is composed of sequential amino acids. Antibodies that bind sequential and nonsequential epitopes generally behave differently and lost of binding occurs when a protein lost its three dimensional conformation structure such as lost of disulfide bond due to a single amino acid substitution of the cysteine residue or denaturation (See page 95, Figure 5, in particular). In fact, the specification on page 11 defines a "variant" of P5CRH polypeptide (SEQ ID NO: 1) as any amino acid sequence that is altered by one or more amino acid residues such that the variant may have "conservative" or "nonconservative" amino acid changes. However, there is no guidance as to which antigenic determinant from the variant or SEQ ID NO: 1 should be use to make antibody that binds to any variant of SEQ ID NO: 1 having at least 90% identity.

At page 8 of the Brief, Appellants argue that the rejection is flawed with respect to chimeric antibodies. There is no requirement that working example be disclosed. There is no requirement that precluded by either the cost or potential adverse effects of an invention. The recited chimeric antibodies can be used, for example, for detect or purify polypeptides which are specifically bound by the recited antibodies (See example XIII of the specification at page 44, lines 29-36).

However, the specification on page 44 lines 29-36 merely mentions the use of anti-P5CRH antibody for purification of naturally occurring or recombinant P5CRH (SEQ ID NO: 1). Although there is no requirement that working example be disclosed, there is no guidance as to the structure such as the amino acid sequence of any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxylate reductase activity. The specification discloses only one polypeptide of SEQ ID NO: 1 having 1-pyrroline-5-carboxylate reductase activities. There is no guidance as to which specific amino acid sequence (epitope) from SEQ ID NO: 1 would generate antibody that binds to any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 and has 1-pyrroline-5-carboxylate reductase activity. Given that the naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 is not enabled, it follows that any antibody such as polyclonal, monoclonal, and chimeric antibody made from said undisclosed polypeptide is not enabled. It also follows that any composition comprising said antibody that binds to any undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 for detection, diagnostic or purification is not enabled.

At page 9 of the Brief, Appellants argue that the Examiner has failed to provide any reasons why one would doubt that the guidance provided by the guidance provided by the present specification would enable one to make and use the recited antibodies which specifically bind to the recited "variants" of SEQ ID NO: 1.

In response, the specification does not teach how to make much less how to use any antibody that binds to any undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxylate reductase activity because there is no guidance as to the specific amino acid sequence used by Appellant to make such antibody that not only binds to SEQ ID NO: 1 but also binds to any undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having 1-pyrroline-5-carboxylate reductase

activity. Further, there is no guidance as to which part of SEQ ID NO: 1 is conserved and which epitope on the undisclosed naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 that the claimed antibody binds. Even if the enzymatic domain is conserved and useful for generating antibody, Kuby *et al,* of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the full-length polypeptide, let alone an antibody that would bind to any natural occurring full-length polypeptide that has at least 31 amino acids difference. Kuby *et al* further teach that some antibody epitope is composed of nonsequential amino acids, far apart in the primary amino acid sequence that have been brought together by the tertiary folding of the protein while other antibody epitope is composed of sequential amino acids. Antibodies that bind sequential and nonsequential epitopes generally behave differently and lost of binding occurs when a protein lost its three dimensional conformation structure such as lost of disulfide bond due to a single amino acid substitution of the cysteine residue or denaturation (See page 95, Figure 5, in particular).

Written description rejection

At page 11 of the Brief, Appellants argue that the "variant" of SEQ ID NO: 1 are described in the specification at for example page 2, lines 30-36, page 5, lines 21-24 and page 12 lines 33-39. In addition, the specification also describes the specific assay to measure PCRH activity on page 43, line 7 to page 44 at line 10. The specification also describes the production of antibodies to P5CRH proteins at page 6, liens 32 to page 7, line 1. Appellants submit that one of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO: 1. Given any naturally occurring polypeptide sequence, it would be routine for one skill in the art to recognize whether it was a variant of SEQ ID NO: 1.

In response, the claims are drawn to antibody that binds to any "variant" of SEQ ID NO: 1 such as any naturally occurring amino acid sequence that is 90% identical to SEQ ID NO: 1. The specification discloses only one polypeptide comprising an amino acid sequence of SEQ ID NO: 1 and an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody and a method of

producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44). Other than the specific antibody that binds to the specific polypeptide comprising SEQ ID NO: 1, there is inadequate written description about the structure of any undisclosed "naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1", much less about the antibody binding specificity, and the antigenic determinant of the claimed antibody binds. Given the lack of a written description of *any* additional representative species of polypeptide such as any "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", and any additional representative species of antibody such as polyclonal, monoclonal, chimeric, single chain, humanized, Fab fragment or $F(ab')_2$ fragment thereof that binds to "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Appellants was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Since the structure of the *any* "naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1" to which the antibody binds and the binding specificity of the claimed antibody are not adequately described, it follows that any composition comprising said antibody is not adequately described. It also follows that the antibody wherein said antibody is labeled is not adequately described.

At pages 12-13 of the Brief, Appellants argue that the present claims specifically define the claimed genus through the recitation of chemical structure. The claims at issue define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. By failing to base its written description inquiry "on whatever is now claimed", the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those not satisfy the written description requirement in Lilly and Fiers.

In response, the claims are drawn to antibody that binds to any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1. There is inadequate written description about the binding specificity, the antigenic determinant of the claimed antibody and the epitope to which the claimed antibody binds. Further, the specification discloses only antibody that binds to only one polypeptide comprising SEQ ID NO: 1 that has 1-pyrroline-5-carboxylate reductase activities. Other than the specific antibody that binds to the specific polypeptide, there is inadequate written description about the structure of any additional "variant" of SEQ ID NO: 1

because there is inadequate written description about which amino acid within the full length polypeptide of SEQ ID NO: 1 can be substitute, delete or add and whether the resulting variant of SEQ ID NO: 1 has 1-pyrroline-5-carboxylate reductase activity, in turn, the antibody generated from the undisclosed variant polypeptide would bind specifically to any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 for any purpose.

At page 14 of the Brief, Appellants argue that the present claims do not define a genus which is "highly variant". The enclosed Brenner et al reference has determined 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. The local identity is particularly important for assessing the significance of the alignments and that greater than 40% identity over at least 70 residues is reliable in signifying homology between proteins (Brener et al, page 6076). The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 (note that SEQ ID NO: 1 has 314 amino acid residues). This variation is far less than that of all potential delta 1-pyrroline-5-carbocylate reductases related to SEQ ID NO: 1, i.e., those short-chain dehydrogenases having as little as 30% identity over at least 150 residues to SEQ ID NO: 1.

In response, the claims are drawn to antibody that binds to *any* naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1. The enclosed Brenner et al reference is irrelevant to antibody binding specificity. The specification discloses only one polypeptide comprising an amino acid sequence of SEQ ID NO: 1. The specification does not describe the amino acid structure of any variant of SEQ ID NO: 1. Further, the specification does not teach which regions or domains of SEQ ID NO: 1 is conserved between protein comprising SEQ ID NO: 1 and any naturally occurring protein having an amino acid sequence at least 90% identical to SEQ ID NO: 1 in terms of enzymatic activity. Even if the variation is far less than that of all potential delta 1-pyrroline-5-carbocylate reductases related to SEQ ID NO: 1, i.e., those short-chain dehydrogenases having as little as 30% identity over at least 150 residues to SEQ ID NO: 1, there is inadequate written description about the antibody binding specificity of the claimed antibody and the epitope to which the claimed antibody binds.

At page 15 of the Brief, Appellants argue that the state of the art at the time of the present invention is further advanced than at the time of the Lilly and Fiers applications. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of proteins and

nucleotides sequences have been complied. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO: 1, and the detail provided by the subject specification, the present inventors were in possession of the claimed antibodies which specifically bind to recited polypeptide variants at the time of filing of this application.

In response, the claims are drawn to antibody that binds to any naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1. The specification discloses only an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody and a method of producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44). Even with these remarkable advances, the mere mentioned of sequence identity or homology is not equal to having the same functions, much less having the same antibody binding specificity as encompassed by the claims.

With the exception of the specific antibody that binds to a polypeptide consisting of SEQ ID NO: 1, there is inadequate written description about the binding specificity, the antigenic determinant of the claimed antibody, much less about the biochemical structure such as the amino acid sequence of any naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1 to which the claimed antibody binds. Other than the specific antibody that binds to the specific polypeptide comprising SEQ ID NO: 1, there is inadequate written description about the structure of any undisclosed "naturally occurring amino acid sequence that is only 90% identical to SEQ ID NO: 1", much less about the antibody binding specificity, and the antigenic determinant of the claimed antibody binds. Given the lack of a written description of *any* additional representative species of polypeptide such as any "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", and any additional representative species of antibody such as polyclonal, monoclonal, chimeric, single chain, humanized, Fab fragment or $F(ab')_2$ fragment thereof that binds to "naturally-occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Appellants was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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